CHAPTER 59

Nerves of the Eye Muscles (III, IV, and VI): Approach to Diplopia

KEY TEACHING POINTS

- In patients with diplopia, the clinician should distinguish monocular diplopia (which persists after closing one eye) from binocular diplopia (which resolves after closing one eye). Monocular diplopia is usually due to problems with the optics of the affected eye (spectacles, contact lenses, cataracts, corneal disease).
- In patients with binocular diplopia, the clinician should first inquire whether there is associated variability of symptoms (myasthenia), ptosis (cranial nerve III palsy, myasthenia), orbital disease or injury (thyroid eye disease, orbital wall fracture), or associated neurologic signs (posterior fossa disease).
- Only after these questions are addressed should the clinician identify which of the 12 eye muscles of a patient with binocular diplopia is weak. First, by moving the eyes through the six cardinal directions of gaze and observing which direction the diplopia is worse, the clinician narrows the diagnostic possibilities to two eye muscles, one in each eye. Then, by using inspection, the red glass test, or the cover/uncover test, the clinician determines which of these two muscles is abnormal.
- Weakness of each specific eye muscle has a unique differential diagnosis (discussed in the text). Almost all of these syndromes can be distinguished at the bedside.

DIPLOPIA

I. INTRODUCTION

Patients with lesions of cranial nerves III, IV, and VI have paralysis of one or more ocular muscles, which prevents the eyes from aligning properly and causes double vision, or **diplopia**. However, the most common mistake in analyzing diplopia is to prematurely conclude that the affected patient must have neuropathy of one of these three nerves. Because less than half of patients with diplopia actually have a cranial neuropathy, this chapter first emphasizes the general approach to *all* causes of diplopia.

II. DEFINITIONS

Diplopia may be monocular or binocular. **Monocular diplopia** persists after occluding one eye. **Binocular diplopia** depends on the visual axes of each eye being out of alignment and therefore disappears when one eye is occluded.

Several other terms are used to describe the findings of patients with binocular diplopia. **Heterotropia** is a general term for the finding of visual axes that are not parallel. (Synonyms are **squint** or **strabismus**.) **Esotropia** means that one eye is converging or is deviated toward the nose (e.g., a left esotropia means that the left eye is deviated toward the nose). **Exotropia** means that one eye is diverging or is deviated toward the temple (e.g., a right exotropia means that the right eye is deviated out). **Hypertropia** means that one eye is deviated upwards (e.g., a left hypertropia means that the left eye is elevated with respect to the right eye). Diplopia may be **horizontal**, with the two images side by side, or **vertical**, with one image higher than the other (the term **vertical diplopia** also encompasses diplopia with images separated both vertically and horizontally).

III. TECHNIQUE

A. GENERAL APPROACH

Fig. 59.1 outlines the general approach to diplopia. The most important initial question is whether the diplopia is monocular or binocular, which can easily be addressed by covering one of the patient's eyes. Overall, 12% to 25% of all diplopia is monocular and 75% to 88% is binocular.[4,5]

In patients with binocular diplopia the clinician can avoid misdiagnosing cranial neuropathy by first addressing the five questions listed in Fig. 59.1. Only after asking these questions should the clinician attempt to identify which eye muscle is weak.

B. IDENTIFYING THE WEAK MUSCLE

When examining the eye muscles, the clinician holds up his or her index finger or penlight and asks the patient to track it toward each of the six cardinal directions of gaze (i.e., left, left and up, left and down, right, right and up, right and down). These directions parallel the principal action of the six eye muscles, as described in Fig. 59.2.

There are two steps in identifying which eye muscle is weak. Step 1 reduces the number of possible weak eye muscles from 12 to 2. Step 2 then identifies which of these two muscles is causing the diplopia.

1. **Step #1: The Worst Diplopia (and Heterotropia) Occurs When the Patient Looks in the Direction of the Weak Muscle.** The clinician asks the patient which of the six cardinal directions aggravates the diplopia the most. According to this rule, the weak muscle is one of the two muscles responsible for this movement, one of which moves the right eye and the other the left eye. For example, diplopia that is worse on far right lateral gaze indicates weakness of the right lateral rectus (LR) or the left medial rectus (MR). Diplopia that is worse when the patient looks to the left and down indicates a problem of the left inferior rectus (IR) or the right superior oblique (SO).*
2. **Step #2 The Clinician Identifies Which of the Two Identified Muscles Is Weak.** There are three techniques (a, b, and c, following):

* Because the actions of the four vertical muscles are sometimes difficult to recall, a mnemonic by Maddox (1907) may be helpful: the affected muscle is "either the same-named rectus muscle or the most crossed-named oblique muscle." For example, if diplopia is worse when the patient looks to the *left* in a *superior* direction, the affected muscles are either the *left superior* rectus or *right inferior* oblique.

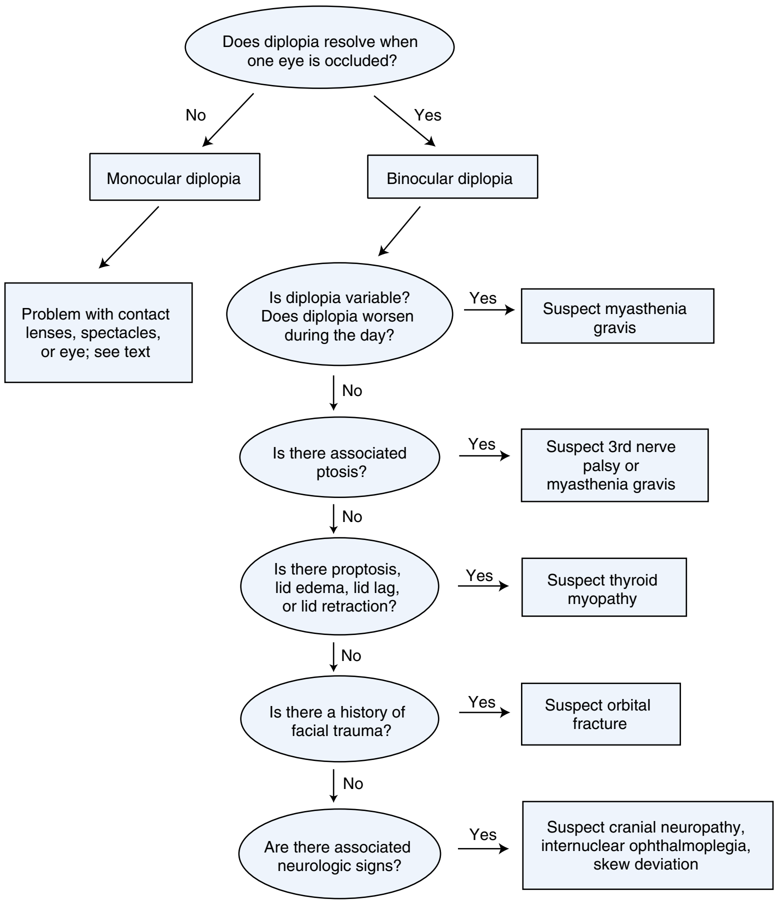


FIG. 59.1 GENERAL APPROACH TO DIPLOPIA. The clinician should first distinguish monocular from binocular diplopia and, in patients with binocular diplopia, address the five questions in the middle of the figure. Only then should the clinician identify which muscle is weak, although this is unnecessary if the clinician already suspects myasthenia (from fatigability) or full third nerve palsy (from weakness of the medial rectus, superior rectus, inferior rectus, and inferior oblique muscles, with or without a dilated pupil). Uncommon causes of diplopia and associated *ptosis*, not presented in the figure, are botulism, the Fisher variant of Guillain-Barré syndrome, and aberrant regeneration of the third nerve.[1,2] Uncommon causes of diplopia and associated *orbital findings* (e.g., proptosis) are carotid-cavernous fistula (which may produce an orbital bruit),[3] orbital tumor, and pseudotumor.

a. **Simple Inspection of the Eyes.** In patients with diplopia on far right lateral gaze, the weak muscle is the right lateral rectus if there is an esotropia, but it is the left MR if there is an exotropia. In patients with diplopia that is worse when looking up and to the right, the weak muscle is the right superior rectus (SR) if there is a left hypertropia but the left inferior oblique (IO) if there is a right hypertropia.

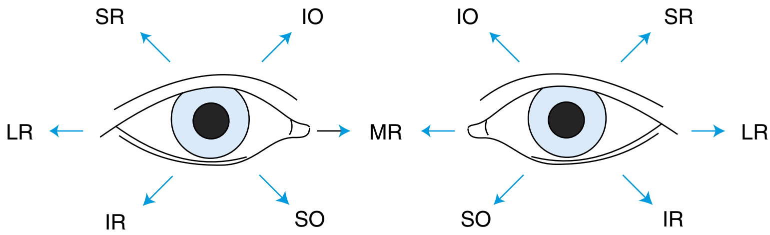


FIG. 59.2 PRINCIPAL ACTIONS OF OCULAR MUSCLES. There are 12 ocular muscles, 6 in each eye. The actions of the medial rectus (MR) and lateral rectus (LR) are simple right and left lateral movements. Although the actions of the four vertical eye muscles—the superior rectus (SR), inferior rectus (IR), superior oblique (SO), and inferior oblique (IO)—are more complex, there is one direction of gaze, indicated in the figure, in which weakness is most apparent.

Often, however, the heterotropia is not obvious, either because the visual axes are out of line by only a degree or two (too small to observe) or because the patient can compensate and temporarily pull the visual axes back into line. In these patients the following techniques are helpful:

b. **The Affected Eye Is the One With the Most Peripheral Image.** By placing a red glass over one eye (usually the right eye), the patient is less likely to fuse the images and, when looking at a penlight in the direction of maximal diplopia, sees two images, one red and one white. The most peripheral image belongs to the weak eye (Fig. 59.3).
For example, in a patient whose maximal diplopia is to the left and down (and who has the red glass over the right eye), the weak muscle is the right SO if the red image is most peripheral but the left IR if the white image is most peripheral.

c. **The Cover/Uncover Test.** To perform this test the clinician covers one eye while the patient looks in the direction of maximal diplopia. Covering one eye prevents fusion of the images, and any heterotropia that exists will return, although it is now obscured by occlusion of the eye. The clinician then observes which way that eye moves to pick up the image after it is uncovered. If it moves out, there was an esotropia; if it moves in, there was an exotropia. If it moves down, that eye had a hypertropia.

IV. CLINICAL SIGNIFICANCE

A. MONOCULAR DIPLOPIA

Almost all patients with monocular diplopia have extraocular or ocular causes.[4,6] Common extraocular causes are the patient's spectacles (e.g., reflections off one or both surfaces of the lenses) or contact lenses (e.g., air bubble in the pupillary area, abnormal curves, or uneven thicknesses). This diplopia resolves after removal of the lenses and, in patients with spectacles, varies as the spectacles are moved in and out or up and down. Common ocular causes include problems in the lens (e.g., fluid clefts, early cataracts), cornea (e.g., astigmatism, keratitis), and eyelids (e.g., chalazion, or prolonged reading which may allow drooping lids to temporarily deform the cornea). The diplopia of these patients resolves when patients look through a pinhole or when a card is held over half of the pupillary aperture (it resolves because the diplopia depends on irregularities of the optic media acting as tiny prisms that

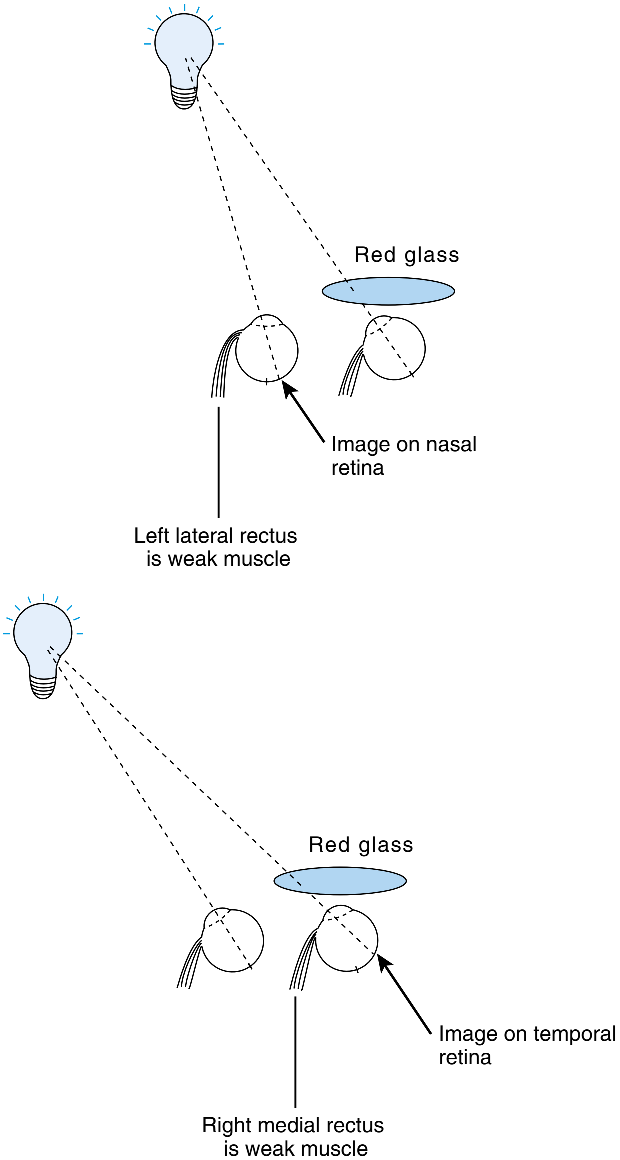


FIG. 59.3 USE OF RED GLASS TO IDENTIFY THE WEAK MUSCLE. In this example, the patient has horizontal binocular diplopia when looking to the left, indicating that the possible weak muscles are either the left lateral rectus or right medial rectus (see Fig. 59.2). A red glass is placed in front of the right eye, causing the image seen by the right eye to be red and that from the left eye to be white. Importantly, images projecting on the nasal side of the retina are perceived to belong to the temporal visual space (see Chapter 58); those on the temporal side retina, to the nasal visual space. If the left lateral rectus is the weak muscle (*top* figure), the image in the left eye falls on the nasal retina, whereas that of the right eye falls on the fovea; therefore the white image is more *peripheral* than the red image (i.e., it is farther leftward in the patient's left visual field). If the right medial rectus is the weak muscle (*bottom* figure), the image in the left eye falls on the fovea and that of the right eye falls on the temporal retina; therefore the red image is more *peripheral* than the white image (i.e., it is farther leftward in the patient's left visual space). In both cases the most peripheral image belongs to the paralyzed eye. In both of these examples, it is the stronger eye that is fixing on the target (i.e., the image falls on the fovea of the stronger eye), but the results are the same if it is the weaker eye that fixates on the object (i.e., the more peripheral image belongs to the weaker eye). See the text.

FIG. 59.4 MYASTHENIA GRAVIS. Myasthenia gravis may mimic any ocular disorder causing diplopia, although most often it mimics weakness of the superior rectus muscle or medial rectus muscle (i.e., difficulty with sustained elevation or adduction of the eye, respectively). Clues to the diagnosis of myasthenia gravis are associated ptosis, fluctuating course, and *normal* pupils.

divert some rays off the fovea; the pinhole or card blocks these wayward rays and thus eliminates the problem).

Rare patients with monocular diplopia have cerebral disease.[7] Despite traditional teachings, hysteria is a rare cause of monocular diplopia.

B. BINOCULAR DIPLOPIA

1. ETIOLOGY

Among patients with binocular diplopia, common final diagnoses are cranial neuropathy (III, IV, or VI; 39% to 67% of patients), eye muscle disease (thyroid ophthalmopathy, myasthenia gravis; 13% of patients), trauma (12%), supranuclear causes (internuclear ophthalmoplegia [INO], skew deviation, 5%), other causes (4% to 16%), and unknown (4% to 11%).[4,5]

2. WEAK MUSCLES AND THEIR CLINICAL SIGNIFICANCE

Incomplete palsies of the third cranial nerve are rare (in one study of 579 third nerve palsies, less than 1% were partial).[8,9] Therefore if only one or two of the third nerve muscles (i.e., SR, IR, MR, and IO) are weak, the diagnosis is almost certainly not a partial third nerve palsy but instead one of the diagnoses listed below.

A. WEAK SUPERIOR RECTUS MUSCLE

The clinician should consider **myasthenia gravis** (Fig. 59.4). Most patients with myasthenia gravis present with ocular symptoms, usually diplopia and ptosis,[10] although the pupils are always normal. Symptoms often fluctuate, worsening at the end of the day or even alternating between the eyes. Ocular myasthenia may mimic any ocular misalignment, although the most commonly affected muscles are the SR or MR muscles, whose weakness is provoked by having the patient sustain upward or far lateral gaze for 30 seconds or more.

One important bedside test for myasthenia is the ice pack test (see the section on Ice Pack Test for Myasthenia Gravis).

B. WEAK INFERIOR RECTUS MUSCLE

The clinician should consider thyroid myopathy and orbital floor fracture.

(1). THYROID MYOPATHY. Patients may have associated proptosis, lid lag, lid retraction, chemosis, and hyperemia at the insertions of the recti muscles (see Chapter 25). These findings are sometimes subtle, and because many patients are also clinically euthyroid, the only finding of thyroid myopathy may be heterotropia. The cause of diplopia is mechanical restriction of the eye muscles, which ophthalmologists confirm using the forced duction test (i.e., after anesthetization of the

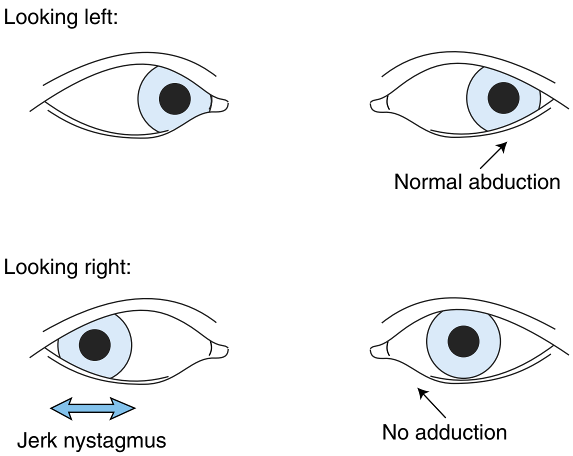


FIG. 59.5 INTERNUCLEAR OPHTHALMOPLEGIA. When the patient in the figure looks to the left (*top* row) both eyes move normally, but when the patient looks to the right (*bottom* row), the left eye fails to adduct ("weak" medial rectus) and the contralateral eye develops a jerk nystagmus. The finding is named for the side with weak adduction (i.e., in this example, a *left* internuclear ophthalmoplegia), and the lesion is in the *ipsilateral* medial longitudinal fasciculus (i.e., *left* medial longitudinal fasciculus in this example). See the text.

conjunctiva, the ophthalmologist grasps the conjunctiva with toothed forceps and attempts to passively rotate the eye, detecting abnormal resistance in patients with thyroid myopathy).[8]

(2). ORBITAL FRACTURE. Diplopia is a complication of 58% of blowout fractures of the orbit and 20% of all midfacial fractures.[11] The heterotropia occurs because of swelling or entrapment of one of the eye muscles, most often the **IR**. In addition to the history of previous trauma, some patients have an additional clue, hypesthesia of the ipsilateral infraorbital area, which results from accompanying injury to the infraorbital branch of the trigeminal nerve. Diplopia may first become a problem for the patient days after the injury, when the swelling has had time to partially resolve.[8]

C. WEAK MEDIAL RECTUS

The clinician should consider INO and myasthenia gravis.

(1). INTERNUCLEAR OPHTHALMOPLEGIA.[12-14] Lesions in the medial longitudinal fasciculus (the periaqueductal pathway in the brainstem that links the nuclei of cranial nerves III, IV, and VI and coordinates conjugate eye movements) cause INO (Fig. 59.5). The features of INO are the following: (1) incomplete adduction of one eye on lateral gaze (i.e., the "weak" MR) and (2) jerk nystagmus of the contralateral abducting eye. Many patients also have vertical nystagmus on upward gaze. The finding is named according to the side with weak adduction. For example, in efforts to look to the far right, if the patient's left eye is unable to completely adduct and the right eye develops a jerk nystagmus, the patient has a left INO (and a lesion in the left medial longitudinal fasciculus).

Ninety-seven percent of patients with *bilateral* INOs have multiple sclerosis, whereas *unilateral* INO has many causes, although the most common one is vertebrobasilar cerebrovascular disease.[13]

(2). MYASTHENIA GRAVIS. Myasthenia gravis (see the section on Weak Superior Rectus Muscle) sometimes causes MR weakness. In contrast to the finding in patients with INO, there is no jerk nystagmus of the abducting eye.

D. WEAK LATERAL RECTUS

Weakness of this muscle almost always indicates damage to the **sixth cranial nerve** (see later), although mimics include myasthenia gravis and thyroid myopathy.[15]

E. WEAK SUPERIOR OBLIQUE

Weak superior oblique indicates damage to the fourth cranial nerve (see later).

F. WEAK INFERIOR OBLIQUE

Weak inferior oblique usually indicates **Brown syndrome**.[16,17] These patients appear to have a weak IO muscle, but the problem actually is in the SO muscle and tendon, which are unable to move freely through their pulley (i.e., the trochlea). In some patients, Brown syndrome is congenital. Acquired Brown syndrome is a complication of orbital inflammation, surgery, and metastases.

3. SKEW DEVIATION

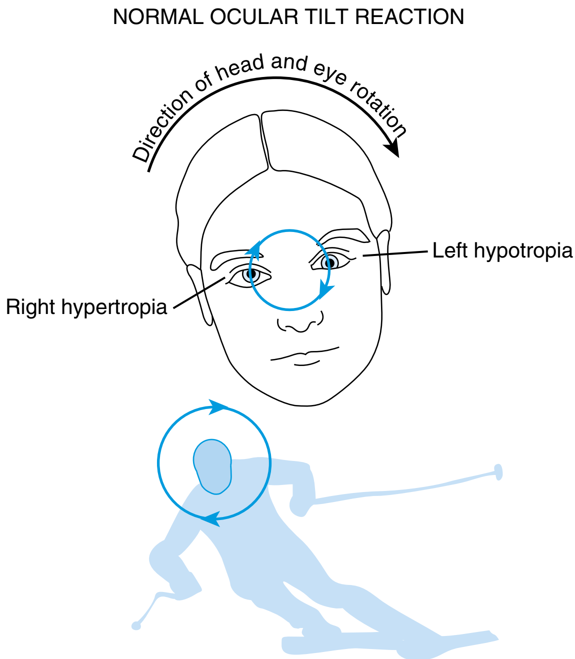
Skew deviation has the following diagnostic features: (1) acquired hypertropia, (2) associated cerebellar or brainstem disease, and (3) lack of alternative etiology for hypertropia. Skew deviation mimics a weak IR 40% of the time, a weak IO 25% of the time, a weak SR 17% of the time, and a weak SO 17% of the time (although the head tilt test, described later, is negative).[8,18]

Skew deviation is believed to represent an abnormal **ocular tilt reaction** (Fig. 59.6),[19] caused by an imbalance in neuronal signals to cranial nerves III, IV, and VI from the right and left otolith organs (utricles). These organs normally sense the position of the patient's head, especially when the patient is upright (i.e., otoliths allow persons to normally detect if they are tilting to the left or right when the eyes closed). Damage to the cerebellum or brainstem may cause input from the utricles to the ocular motor nuclei to be asymmetric, thus producing an abnormal ocular tilt reaction and skew deviation.

Because the utricles are most active when the head is upright and less active when supine, Wong hypothesized that the hypertropia of skew deviation would be more pronounced when the patient is upright than supine.[20] In a study of 125 patients with diverse causes of vertical diplopia, *resolution* of hypertropia after the patient moves from the upright to supine position (i.e., a positive **upright-supine test**) accurately diagnosed skew deviation (sensitivity = 37%, specificity = 100%, positive likelihood ratio [LR] = 73.8, negative LR = 0.6).[21]

C. ICE PACK TEST FOR MYASTHENIA GRAVIS

Clinicians have observed that sunlight may aggravate the ptosis of myasthenic patients and that hot liquids (vs. cold liquids) may provoke myasthenic dysphagia.[22] Based on these observations and that results of electromyography in myasthenia are temperature dependent, Salvedra devised the ice pack test in 1979[23] as a test for ptosis. In this test the clinician places a surgical glove filled with crushed ice for 2 minutes over the patient's closed eye and then compares the ptosis before application of the ice (by measuring the palpebral fissure, i.e., the vertical height of eye opening, to the nearest 0.5 mm) to that after application of the ice. Digital pressure is applied on the forehead just above the eyebrow to avoid contributions from the frontalis muscle in elevating the lid. Because cold temperature improves the weakness of myasthenia, the positive result is *diminished* ptosis after application of the ice (i.e., the palpebral fissure increases 2 mm or more).


NORMAL OCULAR TILT REACTION
Direction of head and eye rotation
Left hypotropia
Right hypertropia

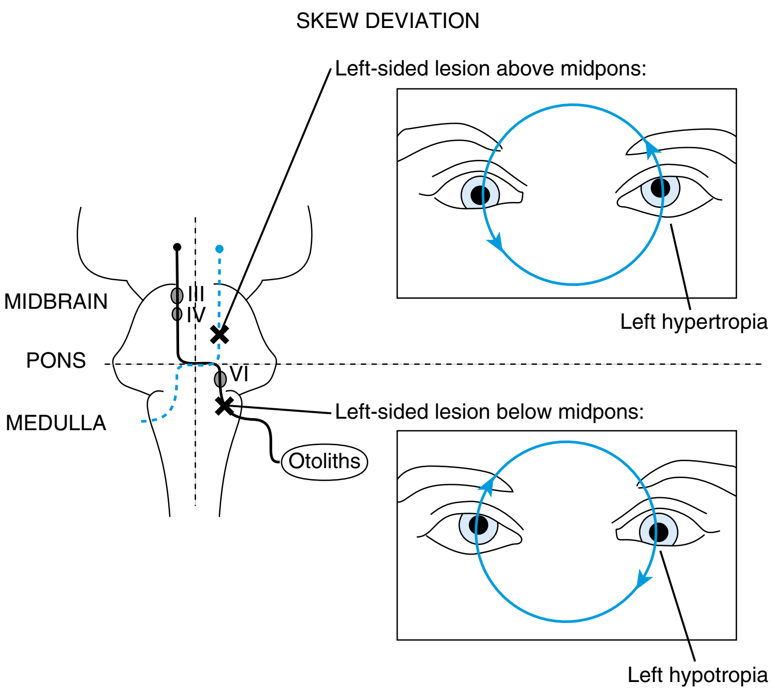

SKEW DEVIATION
Left-sided lesion above midpons:
MIDBRAIN
III
IV
PONS
VI
MEDULLA
Left hypertropia
Left-sided lesion below midpons:
Otoliths
Left hypotropia

FIG. 59.6 SKEW DEVIATION AND THE OCULAR TILT REACTION. When a person leans to one side, his or her head and eyes normally compensate by rotating the opposite direction. For example, in the skier in the top figure, whose body is leaning to the right, the natural compensatory movements are tilting the head to the left, elevation of the right eye and depression of the left eye, and torsion of both eyes (right eye *intorts* and left eye *extorts*), all movements that restore the normal vertical position of the head and eyes (*top* figure). All of these compensatory movements are part of the ocular tilt reaction, a normal reflex that stabilizes retinal images and is mediated by the otolith organs (especially the gravity-sensing utricle and its connections to the ocular motor nuclei and the vestibulospinal tract). Skew deviation (*bottom* figure) is an abnormal heterotropia that appears in disorders (especially cerebellar or brainstem lesions) that produce asymmetry in these pathways.[19] Unilateral lesions below the mid-pons, the point where these gravity-adjusting pathways cross in the brainstem, cause *ipsiversive* tilt reactions (i.e., the patient's *lowermost eye* indicates the side of the lesion; *right bottom;* see Wallenberg stroke in Chapter 62); lesions above the mid-pons cause *contraversive* tilt reactions (i.e., the *uppermost eye* indicates the side of the patient's lesion; *right top*). *III*, Oculomotor nucleus; *IV*, trochlear nucleus; *VI*, abducens nucleus.

Several investigators have studied this test in patients presenting with ptosis, demonstrating that the positive ice test increases probability of myasthenia gravis (LR = 8.3; EBM Box 59.1) and the negative result decreases probability (LR = 0.2). In addition, in two investigations of patients with diplopia (with or without ptosis), the positive ice pack test accurately detected the ophthalmoplegia of myasthenia gravis and distinguished it from other causes of diplopia (positive LR = 30.6, negative LR = 0.1; see EBM Box 59.1). (In these patients, the test was positive if the patient's ophthalmoplegia and diplopia improved after application of ice.)

DISORDERS OF CRANIAL NERVES III, IV, AND VI

I. INTRODUCTION

Table 59.1 reviews the causes of *isolated* palsies of these three cranial nerves, based on analysis of more than 3500 patients reported in the literature. Major causes are ischemic infarcts (all three nerves), intracranial aneurysms (especially the third cranial nerve), head trauma (especially the fourth cranial nerve), and tumors (especially when more than one of these nerves are affected). At least one-fourth of isolated cranial neuropathies affecting these nerves remain idiopathic, even in the modern era of clinical imaging.[40]

II. RULES FOR DIAGNOSING ISCHEMIC INFARCTS

One of the most common causes of *isolated* palsies of cranial nerves III, IV, and VI is ischemic infarction, a diagnosis made at the bedside based on the following criteria: (1) The palsy is isolated (i.e., no other neurologic or ophthalmologic findings), (2) The onset is abrupt, (3) The patient has risk factors for cerebrovascular disease (i.e., age >50 years, hypertension, and diabetes), (4) No other cause is apparent, and (5) The palsy is self-limited (i.e., resolves over several months). Seventy-five percent of ischemic mononeuropathies resolve within 4 months; persistence beyond this should prompt evaluation for other causes.

EBM BOX 59.1
*Ice Pack Test, Detecting Myasthenia**

Finding (Reference)†	Sensitivity (%)	Specificity (%)	Likelihood Ratio‡ if Finding Is Present	Likelihood Ratio‡ if Finding Is Absent
Improvement in ptosis after application of ice[22-31]	77-96	78-98	8.3	0.2
Improvement in diplopia and ophthalmoplegia after application of ice[22,30]	75-97	97-98	30.6	0.1

*Diagnostic standard: for *myasthenia gravis,* a positive edrophonium (Tensilon) test, positive anti-acetylcholine receptor antibody, electromyography, or combinations of these tests.
†Definition of findings: for *Ice Pack test,* see the text. The ice was applied to the eye for 2 minutes[24-26,31] or 5 minutes[22,30] before determining the results of the test.
‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
Click here to access calculator

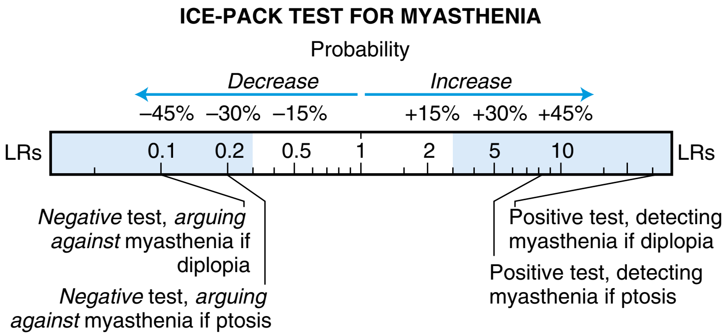


TABLE 59.1 Etiology of Isolated Palsies of Cranial Nerves III, IV, and VI

	Oculomotor Nerve	Trochlear Nerve	Abducens Nerve	Mixed*
PROPORTION (%)†	31	11	45	13
ETIOLOGY (%)				
Head trauma	13	34	11	18
Neoplasm	11	5	19	29
Ischemic	25	22	20	7
Aneurysm	17	1	3	11
Other	14	8	21	19
Idiopathic	20	30	26	16

Based upon references 32-44.
*"Mixed" refers to combinations of cranial nerves III, IV, and VI.
†*Proportion* is ratio of palsies affecting designated cranial nerve to total number of palsies affecting cranial nerves III, IV, and VI.

III. OCULOMOTOR NERVE (CRANIAL NERVE III)

A. THE FINDING

Complete weakness causes downward and outward deviation of the affected eye and ptosis (Fig. 59.7). The pupil may or may not be dilated, depending on the etiology of the patient's neuropathy.

B. CLINICAL SIGNIFICANCE

1. PUPIL-SPARING RULE[45,46]

The most common identified causes of isolated nontraumatic third nerve paralysis are posterior communicating artery aneurysm (which must be managed aggressively) and ischemic infarction of the third nerve (which is managed conservatively). In more than 95% of aneurysmal palsies, the pupil reacts sluggishly to light or is fixed and dilated, but in 73% of ischemic palsies, the pupil is spared.[34,35,37,44,47-58] These observations have led to the pupil-sparing rule, which states that patients with third nerve palsies sparing the pupil do not have aneurysms and can be safely managed expectantly.

Before applying this rule, however, there are three important caveats: (1) The rule applies only to patients with *complete* paralysis of the ocular muscles of the cranial nerve III and *complete* sparing of the pupil. Up to 4% of patients with aneurysms do have sparing of the pupil although the third nerve muscles are only partially paralyzed; (2) The rule should be applied sparingly to patients aged 20 to 50 years, an age-group in which ischemic infarcts are uncommon, and (3) The rule applies only to patients with isolated third nerve palsies. Any other neurologic or ophthalmologic finding (e.g., hemiparesis, proptosis, other cranial neuropathy) invalidates the rule.

Nonetheless, the pupil-sparing rule had greater value in an earlier era when the only diagnostic test for intracranial aneurysms was catheter angiography (a test carrying a 2% risk of stroke), a time when clinicians sought ways to identify those patients who could safely avoid this potentially dangerous test. Today, with the availability of safer noninvasive testing methods (computed tomographic angiography and magnetic resonance imaging), most experts recommend noninvasive vascular imaging of all patients with new-onset isolated nontraumatic third nerve palsies, whether or not the pupil is spared.[59,60]

2. CLINICAL SYNDROMES

Associated findings distinguish the different causes of third nerve palsy.[61]

A. IPSILATERAL BRAINSTEM INJURY

Damage to the third nerve fascicle as it exits the ipsilateral brainstem causes accompanying ipsilateral cerebellar signs (**Nothnagel syndrome**, involving the superior cerebellar peduncle), contralateral hemitremor (**Benedikt syndrome**, involving the red nucleus), or contralateral hemiparesis (**Weber syndrome**, involving the cerebral peduncle).

B. INJURY TO THE NERVE IN THE SUBARACHNOID SPACE

Important causes include uncal herniation (i.e., patient is comatose) and internal carotid-posterior communicating artery aneurysm (i.e., the third nerve palsy is isolated) (see Chapter 21).

C. IPSILATERAL CAVERNOUS SINUS OR ORBIT INJURY

Lesions of the cavernous sinus or orbit cause simultaneous injury to cranial nerves III, IV, and VI (which causes total ophthalmoplegia), to the sympathetic nerves of the iris (contributing to a pupil that is small and unreactive), and to the ophthalmic

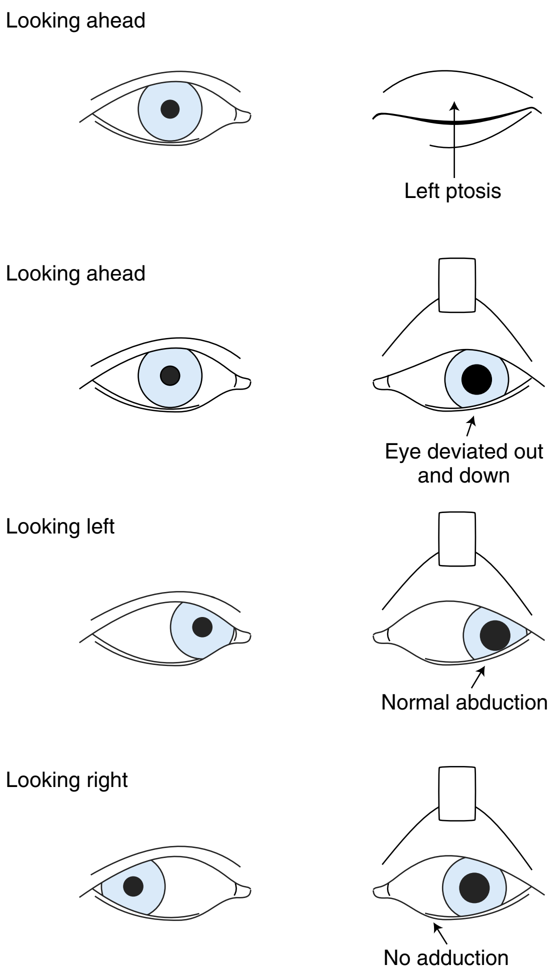


FIG. 59.7 THIRD NERVE PALSY. Complete third nerve palsy (of the left eye in this example) causes ptosis that obscures the position of the eye (*first row*). When the lid is held open (by a piece of tape in this example), the eye appears deviated outward and slightly downward (*second row*) because of unopposed action of the lateral rectus muscle (abducting the eye) and superior oblique muscle (depressing the eye). In this example of third nerve palsy, the pupil is dilated because the cause is an intracranial aneurysm: many ischemic third nerve palsies spare the pupil. (See the section on the Pupil-Sparing Rule in the text.) When the patient looks to the left (*third row*), the intact lateral rectus abducts the eye normally. When the patient looks to the right (*fourth row*), the left eye fails to adduct past the midline. Further tests would also demonstrate that the left eye cannot look up or down.

distribution of the trigeminal nerve (causing hypesthesia of upper third of face). Orbital disease also causes early, prominent proptosis.

D. ISCHEMIC INFARCTS

Ischemic infarction causes isolated third nerve palsy. (See the sections on Rules for Diagnosing Ischemic Infarcts and Pupil-Sparing Rule.)

IV. TROCHLEAR NERVE (CRANIAL NERVE IV)

A. THE FINDING

1. ISOLATED IV PALSY

Paralysis of cranial nerve IV causes vertical diplopia and hypertropia of the affected eye. Nonetheless, the hypertropia may not be evident on examination, and often the clinician will have to tilt the patient's head toward the affected side to bring out the finding (Fig. 59.8). Tilting the head aggravates the diplopia because it requires the ipsilateral eye to intort, which calls upon simultaneous contraction of the SO and SR muscles. These two muscles work together, and the tendency of the SO to depress the eye is normally balanced by that of the SR to elevate the eye. If the SO is weak, however, attempts to intort the eye (e.g., during tilting of the head) instead bring about unopposed action of the SR, which elevates the eye and aggravates the vertical diplopia and hypertropia.

2. COMBINED III AND IV PALSY

In patients with third nerve palsy, testing cranial nerve IV is particular difficult because the eye is already deviated outward and down (see Fig. 59.7). Nonetheless, if cranial nerve IV is intact in these patients, the eye will intort as the patient is asked to look down. Absence of intorsion (which is apparent by observing the medial conjunctival vessels) indicates combined third and fourth nerve palsies. An instructive video of this finding appears in the reference by Reich.[62]

B. CLINICAL SIGNIFICANCE

1. HEAD POSITION

In studies of patients with isolated fourth nerve palsies, 45% actually habitually tilt their head away from the side of the lesion (to minimize any need for intorsion in the affected eye).[39,63,64] This habitual head tilting may be apparent in old photographs of patients with chronic fourth nerve palsies. As expected, when the head is tilted toward the affected side, the diplopia and hypertropia worsen in 92% to 96% of patients.[39,64,65]

2. CLINICAL SYNDROMES

The trochlear nerve has the longest intracranial course of any cranial nerve, in part explaining why trauma is the most common explanation for isolated lesions. Associated findings distinguish the different clinical syndromes.

A. CONTRALATERAL MIDBRAIN INJURY

Associated findings are contralateral Horner syndrome, contralateral dysmetria, and contralateral INO. In all of these syndromes the associated findings are contralateral because the trochlear nerves cross on their way to the eyes (i.e., the fourth cranial nerve innervating the right eye originates in the left brain-stem).[61]

B. IPSILATERAL CAVERNOUS SINUS OR ORBIT INJURY

These lesions cause combinations of findings discussed previously in section on Ipsilateral Cavernous Sinus or Orbit Injury.

C. ISCHEMIC INFARCTS

Ischemic infarction causes isolated fourth nerve palsy. (See the section on Rules for Diagnosing Ischemic Infarcts.)

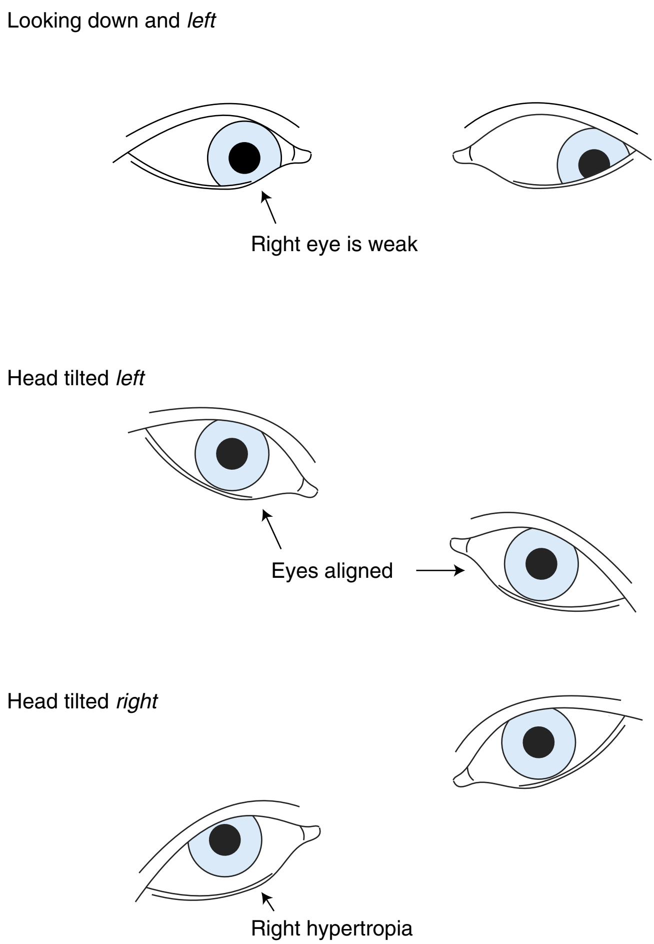


FIG. 59.8 FOURTH NERVE PALSY. The patient in this example has a right fourth nerve palsy. Diplopia is worst when looking down and to the left, indicating that the weak muscle is either the left inferior rectus muscle or right superior oblique muscle (see Fig. 59.2 for principal actions of eye muscles). Simple inspection (*first row*) reveals that the right eye lags behind the left eye, indicating that the weak muscle is indeed on the right side (i.e., right superior oblique). Tilting the head *away* from the affected side (i.e., to the *left* side, away from the weak *right* superior oblique, *second row*) aligns the eyes normally, but tilting the head toward the *affected* side (i.e., to the right side, *third row*) brings out a prominent right hypertropia (i.e., right eye is higher than the left eye). See the text.

V. ABDUCENS NERVE (CRANIAL NERVE VI)

A. THE FINDING

Paralysis of the sixth cranial nerve causes esotropia and an inability to fully abduct the affected eye (Fig. 59.9).

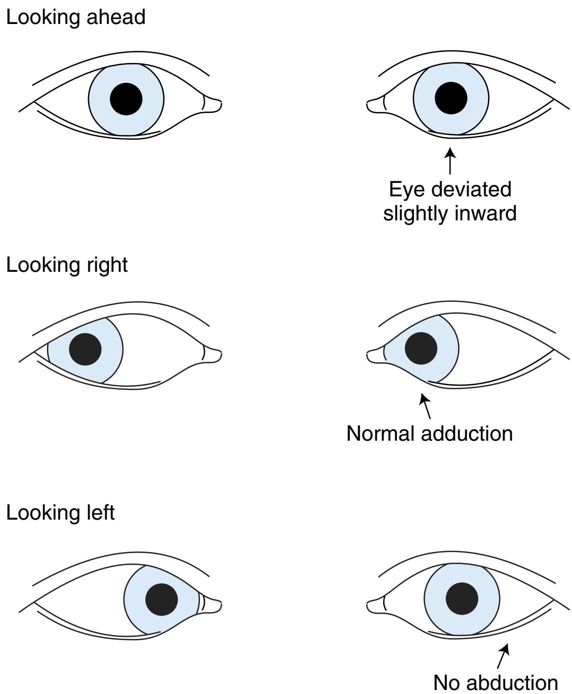


FIG. 59.9 SIXTH NERVE PALSY. When the patient in this example (who has a *left* sixth nerve palsy) looks ahead, there is a mild left esotropia (i.e., left eye is deviated toward the nose, *first row*). When looking to the right, the affected eye adducts normally (*second row*). When looking to the left, the left eye fails to abduct (*third row*).

B. CLINICAL SIGNIFICANCE

The various clinical syndromes are distinguished by their associated findings.

1. **Ipsilateral Pons Injury.** Associated findings are contralateral hemiparesis (Raymond syndrome), ipsilateral seventh nerve palsy and contralateral hemiparesis (Millard-Gubler syndrome), or ipsilateral Horner syndrome, ipsilateral horizontal gaze palsy, and ipsilateral involvement of cranial nerves V, VII, and VIII (Foville syndrome).
2. **Injury to the Nerve in the Subarachnoid Space.** Injury to the nerve in the subarachnoid space often causes isolated sixth nerve palsy. Examples are meningitis, recent lumbar puncture (with subsequent leak of cerebrospinal fluid that leads to stretching of the nerve), and pseudotumor cerebri (also from stretching of the nerve, brought on by elevated intracranial pressure; these patients may have associated papilledema).
3. **Injury at the Petrous Apex.** Examples are complicated otitis media (Gradenigo syndrome, which causes associated ipsilateral decreased hearing, facial pain from involvement of the fifth cranial nerve, and ipsilateral seventh nerve palsy), petrous bone fracture (associated hemotympanum and Battle sign), and nasopharyngeal carcinoma.

4. **Ipsilateral Cavernous Sinus or Orbit Injury.** These lesions cause combinations of findings discussed previously in the section on Ipsilateral Cavernous Sinus or Orbit Injury.
5. **Ischemic infarcts.** Ischemic infarction causes isolated sixth nerve palsy. (See the section on Rules for Diagnosing Ischemic Infarcts.)

The references for this chapter can be found on www.expertconsult.com.

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REFERENCES

1. Forster RK, Schatz NJ, Smith JL. A subtle eyelid sign in aberrant regeneration of the third nerve. *Am J Ophthalmol*. 1969;67(5):696–698.
2. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia, and areflexia). *N Engl J Med*. 1956;255(2):57–65.
3. Henderson JW, Schneider RC. The ocular findings in carotid-cavernous fistula in a series of 17 cases. *Am J Ophthalmol*. 1959;48:585–597.
4. Morris RJ. Double vision as a presenting symptom in an ophthalmic casualty department. *Eye*. 1991;5:124–129.
5. Comer RM, Dawson E, Plant G, Acheson JF, Lee JP. Causes and outcomes for patients presenting with diplopia to an eye casualty department. *Eye*. 2007;21:413–418.
6. Amos JF. Diagnosis and management of monocular diplopia. *J Am Optometric Assoc*. 1982;53(2):101–115.
7. Meadows JC. Observations on a case of monocular diplopia of cerebral origin. *J Neurol Sci*. 1973;18:249–253.
8. Keane JR. Vertical diplopia. *Sem Neurol*. 1986;6(2):147–154.
9. Trobe JD. Isolated third nerve palsies. *Sem Neurol*. 1986;6(2):135–141.
10. Oosterhuis HJGH. The ocular signs and symptoms of myasthenia gravis. *Doc Ophthalmol*. 1982;52(3-4):363–378.
11. Al-Qurainy IA, Stassesn LFA, Dutton GN, Moos KF, El-Attar A. Diplopia following midfacial fractures. *Br J Oral Maxillofac Surg*. 1991;29:302–307.
12. Cogan DG. Internuclear ophthalmoplegia. *Arch Ophthalmol*. 1970;84:583–589.
13. Smith JL, Cogan DG. Internuclear ophthalmoplegia: a review of 58 cases. *Arch Ophthalmol*. 1959;61:687–694.
14. Keane JR. Internuclear ophthalmoplegia. *Arch Neurol*. 2005;62:714–717.
15. Galetta SL, Smith JL. Chronic isolated sixth nerve palsies. *Arch Neurol*. 1989;46:79–82.
16. Wilson ME, Eustis HS, Parks MM. Brown's syndrome. *Surv Ophthalmol*. 1989;34:153–172.
17. Brown HW. True and simulated superior oblique tendon sheath syndromes. *Doc Ophthalmol*. 1973;34:123–136.
18. Keane JR. Ocular skew deviation: analysis of 100 cases. *Arch Neurol*. 1975;32:185–190.
19. Brodsky MC, Donahue SP, Vapiades M, Brandt T. Skew deviation revisited. *Surv Ophthalmol*. 2006;51:105–128.
20. Wong AMF. Understanding skew deviation and a new clinical test to differentiate it from trochlear nerve palsy. *J AAPOS*. 2010;14:61–67.
21. Wong AMF, Colpa L, Chandrakumar M. Ability of an upright-supine test to differentiate skew deviation from other vertical strabismus causes. *Arch Ophthalmol*. 2011;129:1570–1575.
22. Ellis FD, Hoyt CS, Ellis FJ, Jeffery AR, Sondhi N. Extraocular muscle responses to orbital cooling (Ice test) for ocular myasthenia gravis diagnosis. *J AAPOS*. 2000;4:271–281.
23. Saavedra J, Femminini R, Kochen S, de Zarate JCO. A cold test for myasthenia gravis. *Neurology*. 1979;29:1075.
24. Kubis KC, Danesh-Meyer HV, Savino PJ, Sergott RC. The ice test versus the rest test in myasthenia gravis. *Ophthalmology*. 2000;107:1995–1998.
25. Golnik KC, Pena R, Lee AG, Eggenberger ER. An ice test for the diagnosis of myasthenia gravis. *Ophthamology*. 1999;106:1282–1286.
26. Czaplinski A, Steck AJ, Fuhr P. Ice pack test for myasthenia gravis: a simple-noninvasive and safe diagnostic method. *J Neurol*. 2003;250:883–884.
27. Lertchavanakul A, Gamnerdsiri P, Hirunwiwatkul P. Ice test for ocular myasthenia gravis. *J Med Assoc Thai*. 2001;84(suppl 1):S131–S136.
28. Ertaş M, Araç N, Kumral K, Tunçbay T. Ice test as a simple diagnostic aid for myasthenia gravis. *Acta Neurol Scand*. 1994;89:227–229.
29. Sethi KD, Rivner MH, Swift TR. Ice pack test for myasthenia gravis. *Neurology*. 1987;37:1383–1385.
30. Chatzistefanou KI, Kouris T, Iliakis E, et al. The ice pack test in the differential diagnosis of myasthenic diplopia. *Ophthalmology*. 2009;116:2236–2243.
31. Fakiri MO, Tavy DLJ, Hama-Amin D, Wirtz PW. Accuracy of the ice test in the diagnosis of myasthenia gravis in patients with ptosis. *Muscle Nerve*. 2013;48:902–904.

32. Tiffin PAC, MacEwen CJ, Craig EA, Clayton G. Acquired palsy of the oculomotor, trochlear and abducens nerves. *Eye*. 1996;10:377–384.
33. Rush JA, Younge BR. Paralysis of cranial nerves III, IV, and VI. *Arch Ophthalmol*. 1981;99:76–79.
34. Rucker CW. Paralysis of the third, fourth and sixth cranial nerves. *Am J Ophthalmol*. 1958;46(6):787–794.
35. Rucker CW. The causes of paralysis of the third, fourth and sixth cranial nerves. *Am J Ophthalmol*. 1966;61:1293–1298.
36. Berlit P. Isolated and combined pareses of cranial nerves III, IV, and VI: a retrospective study of 412 patients. *J Neurol Sci*. 1991;103:10–15.
37. Green WR, Hackett ER, Schlezinger NS. Neuro-ophthalmologic evaluation of oculomotor nerve paralysis. *Arch Ophthalmol*. 1964;72:154–167.
38. Burger LJ, Kalvin NH, Smith JL. Acquired lesions of the fourth cranial nerve. *Brain*. 1970;93:567–574.
39. Khawam E, Scott AB, Jamplosky A. Acquired superior oblique palsy. *Arch Ophthalmol*. 1967;77:761–768.
40. Richards BW, Jones FR, Younge BR. Causes and prognosis in 4278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves. *Am J Ophthalmol*. 1992;113:489–496.
41. Patel SV, Mutyala S, Leske DA, Hodge DO, Holmes JM. Incidence, associations, and evaluation of sixth nerve palsy using a population-based method. *Ophthalmology*. 2004;111:369–375.
42. Mollan SP, Edwards JH, Price A, Abbott J, Burdon MA. Aetiology and outcomes of adult superior oblique palsies: a modern series. *Eye*. 2009;23:640–644.
43. Park UC, Kim SJ, Hwang JM, Yu YS. Clinical features and natural history of acquired third, fourth, and sixth cranial nerve palsy. *Eye*. 2008;22:691–696.
44. Akagi T, Miyamoto K, Kashii S, Yoshimura N. Cause and prognosis of neurologically isolated third, fourth, or sixth cranial nerve dysfunction in cases of oculomotor palsy. *Jpn J Ophthalmol*. 2008;52:32–35.
45. Trobe JD. Third nerve palsy and the pupil. *Arch Ophthalmol*. 1988;106:601–602.
46. Trobe JD. Isolated pupil-sparing third nerve palsy. *Ophthalmology*. 1985;92:58–61.
47. Zorrilla E, Kozak GP. Ophthalmoplegia in diabetes mellitus. *Ann Intern Med*. 1967;67:968–976.
48. Capo H, Warren F, Kupersmith MJ. Evolution of oculomotor nerve palsies. *J Clin Neuro-Ophthalmol*. 1992;12(1):12–15.
49. Hopf HC, Gutmann L. Diabetic 3rd nerve palsy: evidence for a mesencephalic lesion. *Neurology*. 1990;40:1041–1045.
50. Cogan DG, Mount HTJ. Intracranial aneurysms causing ophthalmoplegia. *Arch Ophthalmol*. 1963;70:757–771.
51. Sanders S, Kawasaki A, Purvin VA. Patterns of extraocular muscle weakness in vasculopathic pupil-sparing, incomplete third nerve palsy. *J Neuro-Ophthalmol*. 2001;21(4):256–259.
52. Fujiwara S, Fujii K, Nishio S, Matsushima T, Fukui M. Oculomotor nerve palsy in patients with cerebral aneurysms. *Neurosurg Rev*. 1989;12:123–132.
53. Kissel JT, Burde RM, Klingele TG, Zeiger HE. Pupil-sparing oculomotor palsies with internal carotid-posterior communicating artery aneurysms. *Ann Neurol*. 1983;13:149–154.
54. Keane JR. Aneurysms and third nerve palsies. *Ann Neurol*. 1983;14(6):696–697.
55. Raja IA. Aneurysm-induced third nerve palsy. *J Neurosurg*. 1972;36:548–551.
56. Botterell EH, Lloyd LA, Hoffman HJ. Oculomotor palsy due to supraclinoid internal carotid artery berry aneurysm. *Am J Ophthalmol*. 1962;54:609–616.
57. Dhume KU, Paul KE. Incidence of pupillary involvement, course of anisocoria and ophthalmoplegia in diabetic oculomotor nerve palsy. *Ind J Ophthalmol*. 2013;61:13–17.
58. Jacobson DM. Pupil involvement in patients with diabetes-associated oculomotor nerve palsy. *Arch Ophthalmol*. 1998;116:723–727.
59. Trobe JD. Searching for brain aneurysm in third cranial nerve palsy. *J Neuro-Ophthalmol*. 2009;29(3):171–173.
60. Volpe NJ, Lee AG. Do patients with neurologically isolated ocular motor cranial nerve palsies require prompt neuroimaging? *J Neuro-Ophthalmol*. 2014;34:301–305.

61. Brazis PW. Isolated palsies of cranial nerves III, IV, and VI. *Sem Neurol*. 2009;29(1):14–28.
62. Reich SG. Teaching video: is it III alone, or III and IV? *Neurology*. 2007;68(21):E34.
63. Urist MJ. Head tilt in vertical muscle paresis. *Am J Ophthalmol*. 1970;69:440–442.
64. Younge BR, Sutula F. Analysis of trochlear nerve palsies: diagnosis, etiology, and treatment. *Mayo Clin Proc*. 1977;52:11–18.
65. Manchandia AM, Demer JL. Sensitivity of the three-step test in diagnosis of superior oblique palsy. *J AAPOS*. 2014;18:567–571.